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ORIGINAL ARTICLE

Population kinetic/pharmacodynamic modelling of the haemodynamic effects of cafedrine/theodrenaline (Akrinor) under general anaesthesia

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Abstract

Aims: The 20:1 combination of cafedrine and theodrenaline (C/T) is widely used in Germany for the treatment of arterial hypotension. Since there is little knowledge about the impact of covariates on the effect, the aim was to develop a kinetic/pharmacodynamic covariate model describing mean arterial pressure (MAP), systolic (SBP) and diastolic blood pressure (DBP), and heart rate (HR) for 30 min after the administration of C/T.

Methods: Data of patients receiving C/T from the HYPOTENS study (NCT02893241, DRKS00010740) were analysed using nonlinear mixed-effects modelling techniques.

Results: Overall, 16 579 measurements from 315 patients were analysed. The combination of two kinetic compartments and a delayed effect model, coupled with distinct Emax models for HR, SBP and DBP, described the data best. The model included age, sex, body mass index (BMI), antihypertensive medication, American Society of Anaesthesiologists (ASA) physical status classification grade, baseline SBP at the time of hypotension and pre-surgery HR as covariates (all $P < .001$). A higher baseline SBP led to a lower absolute increase in MAP. Patients with higher age, higher BMI and lower ASA grade showed smaller increases in MAP. The initial increase was similar for male and female patients. The long-term effect was higher in women. Concomitant antihypertensive medication caused a delayed effect and a lower maximum MAP. The HR increased only slightly (median increase 2.6 bpm, $P < .001$).

Conclusions: Seven covariates with an impact on the effect of C/T could be identified. The results will enable physicians to optimize the dose with respect to individual patients.

KEYWORDS

cardiology, cardiovascular pharmacology, clinical pharmacology, pharmacodynamics, pharmacotherapy, population analysis and modelling and simulation, surgery

1 | INTRODUCTION

Intraoperative hypotension (IOH) is a known risk factor for perioperative morbidity and mortality.[1,2] A number of pharmacotherapies are currently available for the treatment of IOH, including ephedrine and phenylephedrine.[3] In Germany, there is an additional treatment option for IOH: a 20:1 combination of cafedrine and theodrenaline (C/T) is approved for the treatment of anaesthesia-related hypotension as well as hypotension in emergency medicine and is widely used.[4] C/T is composed of noradrenaline and norephedrine, both covalently binding to theophylline.[4] It increases arterial blood pressure (BP) through its effects on preload, contractility and afterload,[4] while heart rate (HR) remains mostly unaffected.[4,5] Previous findings suggest that the rapid onset of action can be attributed to noradrenaline-mediated vasoconstriction. The noradrenaline- and norephedrine-mediated positive inotropic effect is a result of direct and indirect β-adrenoreceptor activation and phosphodiesterase-III inhibition mediated by theophylline.[4,6] Overall, C/T exerts inotropic and moderate vasopressor effects,[4,5] meaning the term "inopressor" best describes its mechanism of action and differentiates this medicinal product from other sympathomimetic agents.

Although C/T was first approved for use in 1963,[4] knowledge regarding the pharmacokinetics and pharmacodynamics of C/T remains limited. The prescribing information of C/T recommends dosage based on clinical effect, suggesting bolus applications of C/T with a maximum daily dose of 600/30 mg C/T.[7] A dose-response study evaluating five dose groups ranging from a median 0.31 to 1.25 mg kg^{-1} cafedrine demonstrated a dose-dependent effect on the mean arterial pressure (MAP).[8] So far, studies have compared only the effect sizes at specific timepoints or the maximum effects after the initial dose.[4,6,8] However, anaesthesiologists frequently administer repeated doses,[9] which renders the analysis of the effect at distinct time points challenging. Here, kinetic/pharmacodynamic (K/PD) modelling using nonlinear mixed-effects modelling techniques, often referred to as population K/PD, allows the analysis of data following time-dependent processes and is frequently applied in drug discovery and development.[10] Modelling can provide comprehensive insights into the understanding of the dose-concentration-response relationship and is advantageous for the analysis of data from patients receiving different dose amounts or repeated doses at different time points. Furthermore, it facilitates the evaluation of the impact of patient specific characteristics on the response to the drug.

The aim of this work was (i) to develop a population K/PD model describing the effect of C/T on MAP, systolic (SBP) and diastolic blood pressure (DBP), and HR, (ii) to explore the impact of clinically relevant covariates on the individual response to C/T, such as patient characteristics, and (iii) to simulate the impact of relevant covariates and various doses on the response to C/T.

What is already known about this subject

- Intraoperative hypotension is a known risk factor for perioperative morbidity and mortality that can be treated with a 20:1 combination of cafedrine and theodrenaline (C/T).
- Knowledge regarding the pharmacokinetics and pharmacodynamics of C/T is limited and so far studies have compared only the effect sizes at specific timepoints or the maximum effects after the initial dose.

What this study adds

- This is the first kinetic/pharmacodynamic model to describe the impact of C/T on haemodynamic parameters over time (specifically mean arterial pressure, systolic and diastolic blood pressure and heart rate).
- Seven patient characteristics ("covariates") were identified that significantly affect the C/T response, comprising baseline systolic blood pressure, body mass index, American Society of Anaesthesiologists physical status classification grade, sex, age, medication with antihypertensive drugs and pre-surgery heart rate (all $P < .001$).
- These findings will assist physicians to optimize the dose based on individual patient characteristics.

2 | METHODS

2.1 | Ethics

The model development is based on data from the HYPOTENS study (NCT02893241, DRKS00010740),[9] which was conducted in compliance with the Declaration of Helsinki and approved by the leading ethics committee at the University of Marburg on 15 April 2016 (Az. 14/16; chairman: Professor Dr. G. Richter). Local ethics committees confirmed the approval to each site. Written consent was obtained from all patients.

2.2 | Study design

The pharmacotherapy C/T (cafedrine hydrochloride 200 mg/theodrenaline hydrochloride 10 mg per 2 mL of solution for injection)

(ratiopharm GmbH) was used in this study.[7] Throughout the manuscript, the dose of C/T administered is expressed in terms of cafedrine only.

A comprehensive description of the study design, participant recruitment and results has previously been provided.[9,11] Briefly, the HYPOTENS study was a prospective, open-label, noninterventional study conducted across multiple centres nationwide. It aimed to compare the treatment of IOH with C/T versus ephedrine in two cohorts. Patient recruitment occurred between July 2016 and December 2017. For the present analysis, only data from the C/T treatment arm of cohort A were used (n = 749 patients). Cohort A contained patients aged ≥50 years undergoing general anaesthesia with propofol and fentanyl (≥0.2 mg or equivalent). The administration of C/T dosage and timing, including multiple doses, was determined individually by the attending anaesthesiologist. The parameters SBP, DBP and HR were recorded prior to anaesthesia induction (pre-surgery), at the time of diagnosis of hypotension (baseline) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 15, 20 25, and 30 min after the first administration. MAP was approximated from the measurements of SBP and DBP as depicted in Equation (1).

$$MAP = DBP + (SBP - DBP)/3 \quad (1)$$

This method for the calculation of MAP can be erroneous at elevated HRs.[12] During surgery, HR remains relatively low and hence this method provides an adequate approximation of the MAP.

Exclusion criteria comprised patients with blood loss of >500 mL during surgery, treatment with hydroxyethyl starch, albumin, gelatine, fresh frozen plasma, erythrocyte concentrate, noradrenaline or other catecholamines, adjustment of patient position to improve venous return flow, reduction of the depth of anaesthesia or the comorbidities pacemaker and haemodynamically significant congenital heart disease (n = 381). Additionally, after visual inspection of the data, patients were excluded from model development if they showed an increase in MAP or SBP by >15 mmHg within 10 min after the initial increase caused by C/T, unrelated to subsequent C/T dosing or any other pharmaceutical or nonpharmaceutical intervention (n = 53). These patients were included in the final model evaluation.

2.3 | Data analysis

Dataset generation, statistical analysis and graphical visualization of the results were performed using R V.4.0.2 (R Foundation for Statistical Computing) and RStudio V.1.4.1103 (RStudio). Model development was performed with nonlinear mixed-effects modelling techniques in NONMEM V.7.4.3 (ICON Development Solutions). Model selection and evaluation criteria included the objective function value (−2 log likelihood), precision of parameter estimates in the form of relative standard errors[13] as well as visual inspection of the goodness-of-fit plots and conditional weighted residuals versus time.[14] Prediction-corrected visual predictive checks (pcVPCs) were performed for model evaluation.

2.4 | Model development

The model was developed stepwise. First, a base model was established describing SBP, DBP and MAP. Second, the effect of C/T on the HR was evaluated based on the model developed for BP. In the absence of direct pharmacokinetic (PK) measurements or established PK models for C/T, we adopted a K/PD modelling strategy. This involved hypothesizing a kinetic model and integrating it with the PD data. We explored various compartment models, including one-, two- and three-compartment configurations with different elimination kinetics, and linked these to the PD effects of C/T on SBP and DBP. Due to the lack of PK data, a volume of distribution was not assessable and was therefore fixed to 1. Various structural models such as turnover models with or without transit compartments as well as direct effect models were tested and linked with different linear, Emax and Hill models to be used as effect and PD models. The model-predicted MAP was calculated from the model predictions of SBP and DBP according to Equation (1). Between subject variability (BSV) was tested on each model parameter. For the description of the HR, different transit, Emax and Hill effect models were linked to the consisting BP model.

Several covariates were considered for testing, including age, weight, height, body mass index (BMI), sex, all haemodynamic parameters pre-surgery and at time of diagnosis of hypotension (baseline), hypertension degree, left heart failure degree according to New York Heart Association (NYHA) classification, comedication with angiotensin II (AT2) antagonistes or angiotensin-converting enzyme (ACE) inhibitors and/or beta-blockers, position during surgery and physical status according to the American Society of Anaesthesiologists (ASA) physical status classification grade. The ASA system classifies the physical status of patients before surgery with grades from 1 (without any pre-existing condition) to 6 (brain-dead and organs are removed for donor purposes). Univariate forward inclusion ($P < .05$) followed by backward elimination ($P < .001$) procedures were used to assess the effect of the covariates. For continuous covariates, we employed power models centred at the population median as defined in Equation (2):

$$P = TV_P \times \left(COV/\overline{COV}\right)^{\theta} \quad (2)$$

Here, P represents the model parameter, TV_P is the typical value of P, COV is the covariate, $\overline{COV}$ is the median of the covariate in the study population, and θ is the estimated covariate effect.

For categorical covariates, the model estimates the fractional change in the parameter caused by different covariate levels. This is exemplified in Equation (3) for the covariate "sex".

$$P = TV_P \times (1 + SEX \times \theta) \quad (3)$$

In this equation, P and TV_P are as previously defined, SEX is the categorical covariate with levels of 0 (male) and 1 (female), and θ is the estimated fractional change in the parameter from the typical value.

The ASA grade was considered as a dichotomous covariate, with grades 3 and 4 grouped together as >2.

2.5 | Simulations

The final population K/PD model was used to simulate the effect of C/T administration and the influence of significant covariates. Covariate values were set to the population median, and their impact was assessed by changing each continuous covariate separately to the 5th and 95th percentiles of the study population or the different values for categorical covariates. The reference was defined based on median characteristics of the study population (female, age 69 years, BMI 25.6 kg m^{-2}, ASA grade 2, no concomitant antihypertensive medication, baseline SBP 82 mmHg, pre-surgery HR 71 bpm). For simulations, patients received a single dose of 50 mg C/T, which represents the most frequently applied single dose in the study. Baseline SBP, DBP and HR were used as baseline values and evaluated for their impact as covariates. To examine the impact of various C/T treatments, the administration of single doses of 40, 50 and 100 mg of C/T and of 2 × 50 mg of C/T at minutes 0 and 8 was simulated. Here, 40 and 100 mg of C/T represent the second and third most applied single-dose amounts. For multiple-dose applications, the second dosing occurred after a median of 8 min, with a median of 50 mg of C/T.

Additional simulations were performed to explore the combination of various covariate levels for the most impactful covariates BMI, age and concomitant antihypertensive medication.

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/24.

3 | RESULTS

3.1 | Description of dataset

The final dataset included 315 patients. Table 1 provides a detailed overview of the analysis population. The median first dose was 50 mg of cafedrine (range 20-200 mg) and the median follow-up dose was 50 mg of C/T (range 20-100 mg). In total, 132 patients (41.9%) received only one dose and 183 patients (58.1%) received two or more doses, with a median time span between doses of 8 min. Patients with antihypertensive medication had a higher likelihood of receiving multiple dosing and thus a higher risk of an inadequate increase of BP after the first dose than patients without antihypertensive medication (87 of 144 patients [60.4%] with comedication and 108 of 224 [48.2%] patients without comedication receiving multiple dosing, risk ratio 1.25, $P = .0196$).

TABLE 1 Characteristics of the study subjects used for model development.

Characteristic	Unit/value	Median (range) or n (%)
Weight	kg	75.0 (48.0 to 178.0)
Height	cm	169 (151 to 196)
BMI	kg m^{-2}	25.6 (17.0 to 54.9)
Sex	Male	142 (45.1%)
	Female	173 (54.9%)
Age	Years	69.3 (52 to 96)
Baseline SBP	mmHg	82 (50 to 144)
Baseline DBP	mmHg	50 (22 to 73)
Baseline MAP	mmHg	66.5 (36.5 to 97.5)
Baseline HR	bpm	60 (36 to 132)
Pre-surgery SBP	mmHg	142 (85-211)
Pre-surgery DBP	mmHg	79 (45-114)
Pre-surgery MAP	mmHg	110 (71-157)
Pre-surgery HR	bpm	71 (45-140)
Medication with beta-blockers[a]	Yes	82 (26.0%)
	No	233 (74.0%)
Medication with ATII/ACE[a]	Yes	70 (22.2%)
	No	245 (77.8%)
ASA classification grade	2 (mild systemic disease)	207 (65.7%)
	3 (severe systemic disease)	107 (34.0%)
	4 (severe systemic disease that is a constant threat to life)	1 (0.3%)
NYHA classification	Not applicable	294 (93.3%)
	Class 1	3 (1.0%)
	Class 2	14 (4.4%)
	Class 3	4 (1.3)
First dose	mg cafedrine	50 (20-200)
Total dose[b]	mg cafedrine	100 (20-400)

Abbreviations: ACE, angiotensin converting enzyme inhibitor; ASA, American Society of Anaesthesiologists; ATII, angiotensin II antagonist; BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; NYHA, New York Heart Association; SBP, systolic blood pressure.

[a]Concomitant medication continued on the day of surgery.

[b]Sum of all dose amounts received by each individual.

3.2 | Population K/PD model

The effect of C/T on SBP, DBP, and HR was best described by a two-compartment kinetic model coupled with a delayed effect model as depicted by Equations (4)-(10), where the dose amount (included as the amount of cafedrine) is administered into compartment A1. The model is schematically depicted in Figure 1. The full NONMEM model code can be found in the **Supporting information**.

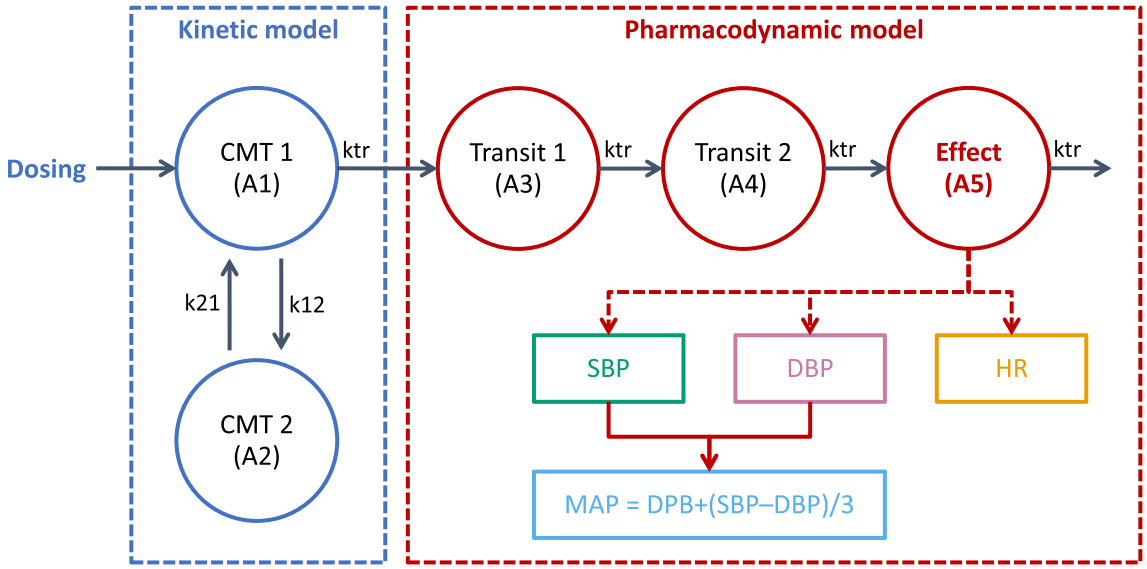

FIGURE 1 Schematic representation of the model. CMT, compartment; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure.

$$d/dt(A1) = -k12 \times A1 + k21 \times A2 - ktr \times A1 \quad (4)$$

$$d/dt(A2) = k12 \times A1 - k21 \times A2 \quad (5)$$

$$d/dt(A3) = ktr \times (A1 - A3) \quad (6)$$

$$d/dt(A4) = ktr \times (A3 - A4) \quad (7)$$

$$d/dt(A5) = ktr \times (A4 - A5) \quad (8)$$

$$SBP = BL\_SBP + (MAX\_SBP - BL\_SBP) \times A5/(A5 + ED50\_SBP) \quad (9)$$

$$DBP = BL\_DBP + (MAX\_DBP - BL\_DBP) \times A5/(A5 + ED50\_DBP) \quad (10)$$

$$HR = BL\_HR + (MAX\_HR - BL\_HR) \times A5/(A5 + ED50\_HR) \quad (11)$$

The MAP model predictions were approximated based on the model predictions for SBP and DBP according to Equation (1).

The transit compartments describe the delay between the bolus application of C/T and the maximum effect, with a mean transit time of 4.04 min. Due to the lack of PK data, it was not possible to distinguish between the transit rate (ktr) and the elimination rate of the kinetic compartment. Hence, elimination from compartment A1 occurred with rate ktr. Emax models were used to calculate SBP, DBP and HR based on the amount in compartment A5 (Equations (9)-(11)). For each haemodynamic parameter, different maximum parameter levels (MAX) and half maximal effective C/T amounts (ED50) were estimated. The maximal increase was calculated as the difference between the baseline (BL) and MAX for each haemodynamic parameter.

With a median relative increase of 138% (MAX_SBP 195 mmHg with a median baseline SBP of 82 mmHg) and an ED50 of 2.09 mg C/T, SBP shows a more sensitive reaction to C/T than DBP, with a 126% median relative increase and an ED50 of 2.4 mg C/T ($P < .001$). After C/T application the HR increased on average by 1.5% with an ED50 of 1.39 mg C/T ($P < .001$). A proportional model was used to describe the residual error (9.22%).

BSV was identified in the transit rate (ktr, 64.5% coefficient of variation [CV]) and the maximum effects on SBP, DPB and HR (MAX_SBP, MAX_DBP and MAX_HR). The BSV on the maximum effects of SPB and DBP were highly correlated and could be described using the same parameter (MAX_SBP and MAX_DBP 37.5%CV, and MAX_HR 30.7%CV). Baseline SBP, BMI, ASA grade, sex, age, medication with antihypertensive drugs and pre-surgery HR were identified as significant covariates (all $P < .001$). All model parameter estimates are shown in Table 2.

Baseline SBP, BMI and ASA grade were identified as significant covariates on the distribution rate from the peripheral compartment of the kinetic model (k21). A change from 80 to 90 mmHg in baseline SBP resulted in a 31% drop in k21. A change from a BMI of 25 to 30 kg m^{-2} resulted in a 20% drop in k21. Patients with ASA grade >2 had a 38% higher k21 in comparison to patients with ASA grade ≤2. The sex of patients also impacted k21 as well as the ED50 of the HR (ED50_HR): female patients had a 47% higher k21 and a 182% higher ED50_HR than male patients.

In our study, we categorized concomitant antihypertensive medication into two groups: (a) beta-blockers and (b) AT2 antagonists or ACE inhibitors. These were initially included as separate covariates in the model. However, our analysis showed that treating these groups as distinct covariates or combining them into a single category did not significantly enhance the model's performance or parameter

TABLE 2 Model parameters of the final model.

Parameter	Parameter description	Unit	Estimate (RSE)
K/PD model			
k12	Rate constant to peripheral compartment	min^{-1}	8.94 (12%)
k21	Rate constant from peripheral compartment	min^{-1}	0.051 (7.1%)
ktr	Transit rate from central compartment to delayed effect	min^{-1}	0.495 (5.7%)
k12(age)	Exponent of age effect on k12	[a]	−2.77 (20%)
k21(BL_SBP)	Exponent of baseline SBP effect on k21	[a]	−3.18 (7.5%)
k21(BMI)	Exponent of BMI effect on k21	[a]	−1.21 (14.3%)
k21(ASA)	k21 change for ASA grade>2	[a]	0.38 (26.3%)
k21(sex)	k21 change for female sex	[a]	0.469 (21.1%)
ktr (medication)	ktr change for antihypertensive medication	[a]	−0.254 (0.1%)
BSV ktr	Between-subject variability ktr	%CV	64.5 (4.5%)
SBP effect model			
MAX_SBP	Maximum SBP	mmHg	195 (4%)
ED50_SBP	C/T amount causing half maximal SBP increase	mg	2.09 (12.5%)
ED50_SBP (age)	Exponent of age effect on ED50_SBP	[a]	3.38 (21.1%)
BSV MAX_BP	Between subject variability MAX_BP	%CV	37.5 (5.5%)
DBP effect model			
MAX_DBP	Maximum DBP	mmHg	113 (43.9%)
ED50_DBP	C/T amount causing half maximal DBP increase	mg	2.4 (12.3%)
ED50_DBP(age)	Exponent of age effect on ED50_DBP	[a]	4.75 (11.2%)
BSV MAX_BP	Between subject variability MAX_BP	%CV	37.5 (5.5%)
HR effect model			
MAX_HR	Maximum HR	bpm	62.9 (2.1%)
ED50_HR	C/T amount causing half maximal HR increase	mg	1.39 (22.7%)
ED50_HR(sex)	ED50_HR change for female sex	[a]	1.82 (31.6%)
ED50_HR(medication)	ED50_HR change for antihypertensive medication	[a]	−0.47 (3.3%)
MAX_HR(HR_PS)	Exponent of pre-surgery HR effect on MAX_HR	[a]	0.792 (14.8%)
BSV MAX_HR	Between subject variability MAX_HR	%CV	30.7 (9.5%)
PE	Proportional error for all haemodynamic parameters	%	9.22 (0.6%)

Abbreviations: ASA, American Society of Anaesthesiologists; BMI, body mass index; BSV, between subject variability; comedication, beta-blockers, angiotensin II antagonists or angiotensin converting enzyme inhibitors; C/T, cafedrine/theodrenaline; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; PS, pre-surgery; RSE, relative standard error; SBP, systolic blood pressure.
[a]Unitless parameter.

identifiability. Consequently, we employed an additive effect model, assigning an equal effect size to medication from either group. This approach revealed that concomitant medication influenced the transit rate (ktr) and the ED50 for HR (ED50_HR) in our pharmacodynamic model. Specifically, patients with one antihypertensive drug exhibited a 25% lower ktr and a 57% lower ED50_HR compared to those without such medication. The age of the patients impacted the distribution rate to the peripheral compartment of the virtual PK model (k12) and the ED50 values for SBP and DBP. Patients aged 60 years had a 54% higher k21 than patients aged 70 years (13.2 and 8.59 min^{-1}, respectively). For patients aged 60 and 70 years, ED50_DBP was 1.24 and 2.57 mg C/T, respectively, and ED50_SBP was 1.3 and 2.19 mg C/T, respectively. The pre-surgery HR influenced the maximum HR reached after dosing of C/T (MAX_HR). A pre-surgery HR change from 70 to 80 bpm resulted in an increase in MAX_HR from 62 to 69 bpm ($P < .001$).

Observations and model descriptions for the haemodynamic parameters of six randomly drawn patients (Figure 2) highlight the good model performance while underlining the high variability between and within patients. In particular, HR shows high short-term intra-individual variability that cannot be explained by the drug effect. Nonetheless, the pcVPC (Figure 3) and goodness-of-fit plots (Supporting Information Figure S1) display the good descriptive performance of the model without a visible trend. Supporting Information Figure S2 furthermore shows a pcVPC stratified by dose for patients that received only one dose of C/T. Here, 22, 74 and 19 patients received a single dose of

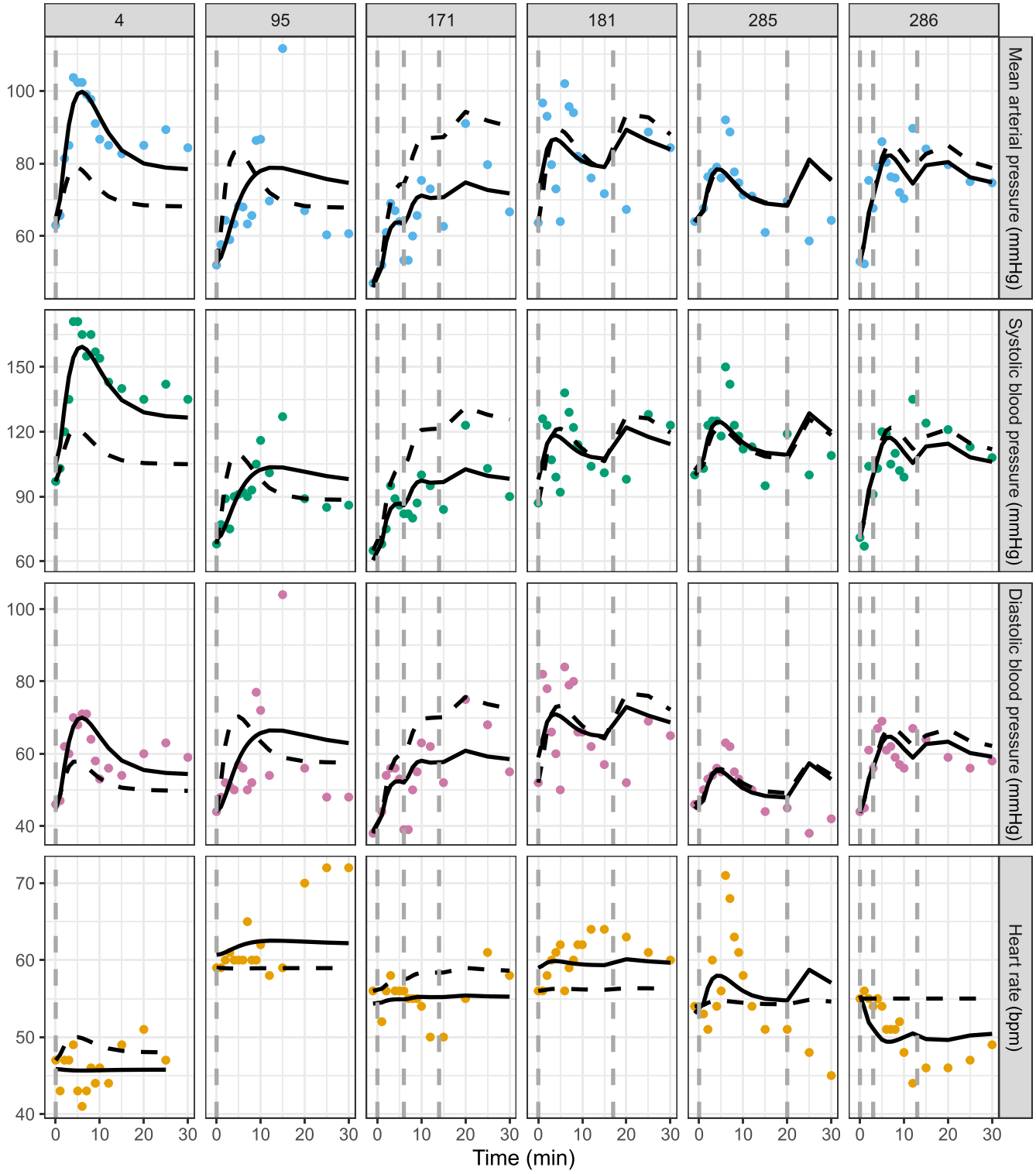

FIGURE 2 Exemplary plots of randomly drawn patients. Points indicate observations, full lines indicate individual model predictions and dashed lines indicate population predictions. Vertical, grey dashed lines indicate the time points of dose administrations.

40, 50 and 100 mg of C/T, respectively. A slight underprediction of the data is observed. However, this underprediction is likely caused by the creation of the subset of the data as patients who did not react to the first C/T dose with an adequate MAP increase (and therefore received a second dose) were excluded from the observations.

3.3 | Simulations

To visualize the impact of the covariates on the model predictions, simulations were performed by varying one covariate or dosing at a time based on the reference patient (Figure 4). Supporting Information

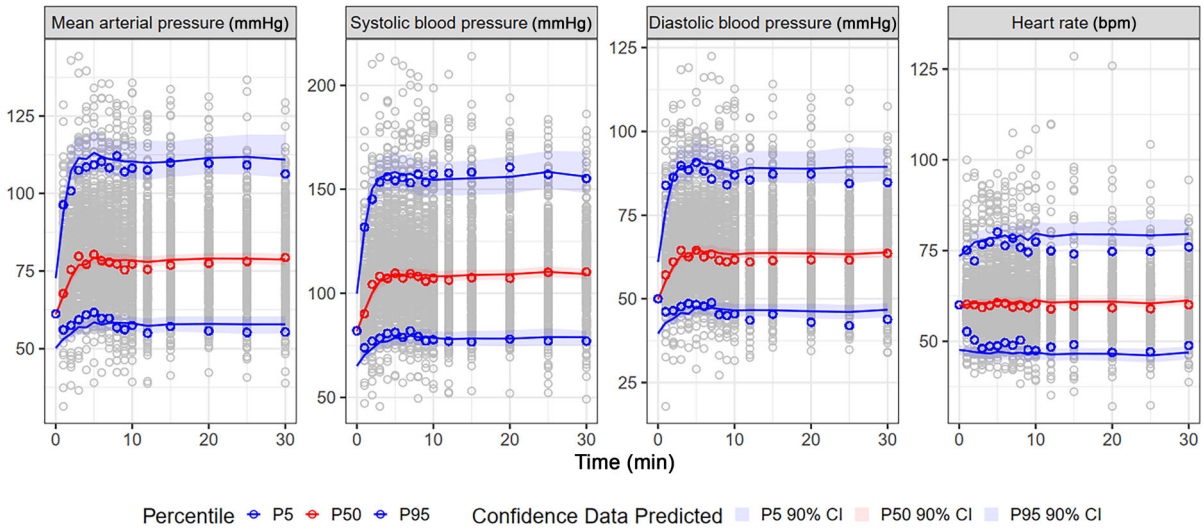

FIGURE 3 Prediction-corrected visual predictive check. Points indicate observations, lines and bands indicate model predictions. P5, P50 and P95: 5th, 50th and 95th percentiles. CI, confidence interval.

Figure S3 shows the results of the same simulation extended for DBP and SBP.

Figure 4A shows that with increasing dose, MAP increases significantly ($P < .001$) while changes in HR were small. Similar MAP was reached after 30 min in both 2 × 50 mg C/T and 1 × 100 mg C/T simulations.

The effect of C/T was mitigated in older patients (Figure 4B). In patients with higher BMI the effect was similar until approximately 4 min after initial C/T application and lower after reaching maximum MAP when compared to patients with lower BMI (Figure 4C). Female patients and patients with ASA grade >2 reached similar peak MAP but higher final MAPs than male patients and patients with ASA grade 2, respectively (Figure 4D,E).

A lower baseline SBP resulted in lower baseline MAPs and the absolute change in MAP decreased with higher baseline SBPs (Figure 4F). However, peak MAPs were similar independent of baseline SBP.

Antihypertensive medication delayed and lowered the peak MAP: without medication the maximum increase was 22.4 mmHg after 5 min (Figure 4G). With one and two antihypertensive drugs, the maximum increase was 19.2 mmHg after 6.5 min and 15.7 mmHg after 11 min, respectively.

The effect of C/T on the HR was slightly pronounced by antihypertensive medication in male patients and in patients with a high pre-surgery HR (Figure 4H). The simulated median effect of C/T on the HR was 2.6 bpm ($P < .001$).

Additionally, simulations were performed for each combination of age (55, 65, 75 and 85 years), BMI (20, 25, 30 and 35 kg m^{-2}) and 0 or 1 antihypertensive comedication for two dose groups (50 and 100 mg C/T single dose). The results are shown in Supporting Information Figure S4. Here, simulations show that the average increase of MAP in the first minutes is similar in patients receiving 50 mg of C/T (black solid lines) to patients receiving 100 mg of C/T and comedication with antihypertensive medication (green dashed lines). However, peak MAPs were higher in patients receiving 100 mg of C/T and comedication.

4 | DISCUSSION

Our analysis presents the novel mathematical K/PD model which describes the impact of C/T on the BP and HR accurately over time. Previous studies only performed statistical analyses comparing the effect of C/T at specific time points, which renders the analysis of multiple dosing at different time points impossible.[4,8] However, the analysis of the impact of multiple dosing of C/T is highly relevant, as it occurs frequently in clinical practice. For example, about half of the patients from the HYPOTENS study received two or more doses.[12] By employing nonlinear mixed-effects modelling, we were able to synchronously analyse the effects of C/T in patients receiving different dose amounts at various time points.

The available knowledge regarding the PK properties of C/T is limited. Cafedrine has a half-life of approximately 60 min.[7] No data on the half-life of theodrenaline are available due to its dosage being below the detectable limit.[7] Furthermore, no previously developed PK models are available for cafedrine or theodrenaline. Consequently, it was not possible to describe the PK of each component separately nor distinguish between the effects of the two components of C/T. Nonetheless, the utilization of a kinetic model as input for the subsequent PD models has proven successful in this study and previous approaches.[15]

A two-compartment model, characterized by rapid initial distribution and a terminal half-life of 4.34 h, most effectively described the data in our study. This terminal half-life is consistent with the half-life of norephedrine (4 ± 0.5 h), a metabolite of cafedrine, which is also optimally described by a two-compartment model.[16] Additionally,

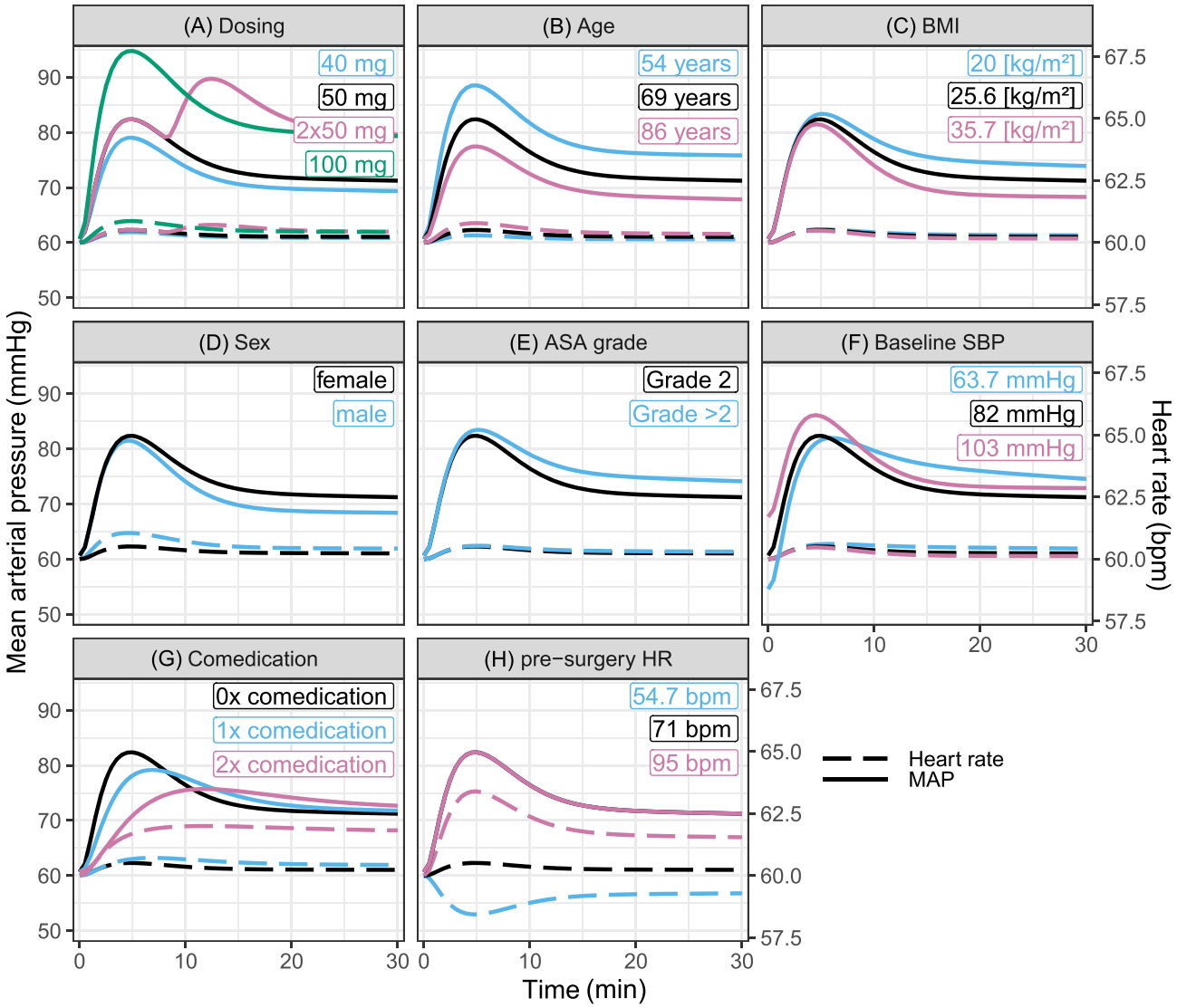

FIGURE 4 Simulations of covariate and different dosing effects. 0x, 1x and 2x comedication refers to no antihypertensive medication and medication with beta-blockers or/and angitensin II antagonists/angiotensin converting enzyme inhibitors, respectively. Dose amounts refer to the cafedrine component of cafedrine and theodrenaline (C/T). In scenario H, the covariate only influences the heart rate (HR) and not the mean arterial pressure (MAP), hence model predictions for MAP overlap and appear as one line. ASA, American Society of Anaesthesiologists; BMI, body mass index; SBP, systolic blood pressure.

theophylline, a metabolite of both cafedrine and theodrenaline, has a documented half-life of 6-9 h in nonsmokers and 3-6 h in smokers.[17] Although utilizing a two-compartment model in K/PD model development is not typically considered state-of-the-art,[18,19] in this particular case of modelling a combination of two drugs with active metabolites such an approach was deemed justified due to its significant enhancement of data representation.

Furthermore, while more mechanistic models for the description of MAP and HR, along with other haemodynamic parameters, have been developed previously,[20–22] our attempts to establish a highly mechanistic model, incorporating the effects of each drug component with separate pharmacokinetic models and dependencies between BP and HR, were unsuccessful. The complexity of the actions of C/T, which include both synergistic and antagonistic effects on heart muscle and vascular smooth muscle cells, precluded the use of existing models or the development of a new, more intricate model. Consequently, our K/PD model, which employs classical Emax-effect models, emerged as the best solution. It offered the most identifiable model parameters and the clearest representation of our data, effectively navigating the complexities inherent in this pharmacological study. However, it is noteworthy that the interindividual variability might not be captured reliably with such a model.

Previously identified covariates that impact the C/T K/PD relationship were baseline BP, sex and antihypertensive medication, all of which were confirmed by our findings. In our study as well as in a previous study,[8] a higher baseline pressure resulted in a smaller absolute increase in MAP. Females exhibited a more pronounced increase in MAP after 10 min, which is consistent with other studies showing a

higher increase in MAP in female patients.[8,23] The underlying mechanisms for sex-specific differences are multifactorial.[23] Differences in the beta-adrenergic reactivity might be attributed to the effect of oestrogen and different speed of the down-regulation of beta-adrenergic responsiveness in ageing male and female patients.[24]

Patients receiving beta-blockers and/or AT2 antagonistes or ACE inhibitors demonstrated a slower increase in BP with lower peaks but similar long-term increases in BP. These findings align with previous results[8,23] showing that beta-blocking agents prolong the time until a 10% MAP increase is reached. As the effect of C/T is in part mediated via β-adrenoreceptor activation, it was anticipated that patients receiving comedication effecting the β-adrenoreceptor would respond differently to treatment with C/T.

Furthermore, BMI, age and ASA grade were identified as covariates impacting the response to C/T for the first time. Higher BMI was associated with a mitigated response, possibly due to a higher volume of distribution. Older patients exhibit a lower rise in MAP, which is presumably caused by the decrease in beta-adrenergic responsiveness with advancing age.[25] Patients with ASA grades >2 reach higher final MAPs. Given that the ASA classification considers various disease-related parameters when assigning grades,[26] it was not possible to determine which specific parameters contribute to the increased sensitivity towards C/T.

Previous studies[8,15] observed a mitigated effect of C/T in patients with NYHA ≥1 that could not be reproduced in the presented analysis. However, this might be attributed to the small number of patients with heart failure in our study dataset (n = 21, 6.7%).

In comparison to other drugs administered for the treatment of hypotension, C/T has the advantage of having little to no effect on the HR.[12] Nonetheless, our model revealed a significant but clinically negligible effect on HR, with a median change of 2.6 bpm. The inclusion of the pre-surgery HR as a covariate on the maximum effect on the HR (MAX_HR) led to a significant reduction in the interpatient variability on MAX_HR by more than one-third (30.7%CV with *vs* 47.7%CV without covariate). Hence, after C/T administration the HR changes towards patient individual levels measured before surgery. Furthermore, sex and concomitant antihypertensive comedication exerted small but significant influences on the effect of C/T on HR.

Although the effect of some covariates is small individually, their combined influence can result in clinically relevant changes. Overall, the covariates BMI and age are each correlated significantly to ASA grade and antihypertensive medication. However, these correlations are weak (Pearson correlation coefficient <0.31) and the effect size of each covariate stayed the same, independently of the inclusion or exclusion of the respective correlated covariate. Hence, all covariates were retained in the model despite minor correlations.

The limitations of this analysis stem from the limited availability of data regarding the PK of C/T, therefore the model describes the overall effect-time course of the combination. Hence, despite the successful application of a K/PD model in this analysis, future trials and analyses could benefit from bioanalytical measurements. A further limitation arising from the hybrid nature of the K/PD model is that the distinction between covariate effects on the kinetic system versus the pharmacodynamic system is not straightforward. Consequently, we interpreted the impact of covariates based on their observed effects in the simulations rather than strictly interpreting them based on traditional kinetic or pharmacodynamic principles. This method allowed us to explore the potential influence of various covariates on the model's behaviour, even in cases where their impact might not be immediately intuitive.

Nevertheless, the developed model might close a knowledge gap regarding the individualized effect of C/T and assist physicians in selecting the appropriate dose to ensure the desired increase in the BP, thereby reducing the need for multiple dosing. Here, the visualization of the impact of antihypertensive comedication can improve the understanding of the trajectory of the BP after C/T, where the increase in the BP takes more time in patients with antihypertensive medication. Hence, the simulations can help the decision making with respect to the need for multiple dosing of C/T.

In the presented study, C/T was administered as an intravenous bolus application. However, providing clinicians with the option to administer C/T via continuous infusion is likely to be advantageous.[27] In contrast to previous analyses where the impact of C/T on BP was only analysed after single-dose administration and at distinct time points, this model presents the possibility of being applied for the description of BP after continuous application of C/T.

In summary, this is the first K/PD model to describes the impact of C/T on haemodynamic parameters over time. Seven covariates were identified that significantly affect the C/T response. These findings can assist physicians to optimize the dose based on individual patient characteristics.

AUTHOR CONTRIBUTIONS

Formal analysis: C.D. *Investigation and methodology*: C.D., T.L. and S.K. *Project administration*: S.H.-L. and M.M. *Visualization*: C.D. *Writing—original draft*: C.D., T.L. and S.K. *Writing—review and editing*: B.V., C.G., T.K., L.E., S.H.-L. and M.M.

CONFLICT OF INTEREST STATEMENT

C.D. is an employee of Saarmetrics. B.V., T.K. and L.E. have received honoraria from ratiopharm GmbH. C.G. has no conflicts of interest to declare. S.H.L. is an employee of ratiopharm GmbH. M.M. is an employee of TEVA GmbH. T.L. and S.K. are shareholders of Saarmetrics.

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DATA AVAILABILITY STATEMENT

Qualified researchers may request access to patient-level data and related study documents, including the study protocol and the statistical analysis plan. Requests will be reviewed for scientific merit, product approval status and conflicts of interest. Patient level data will be de-identified and study documents will be redacted to protect the privacy of trial participants and to protect commercially confidential information. Please email (usmedinfo@tevapharm.com) to make your request.

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